PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12390730/EJH/sxk	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001723	International Filing Date *(day/month/year)* 23 December 2003	Priority Date *(day/month/year)* 23 December 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] C12N 15/90 15/85 15/79 15/12

Applicant

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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand 17 June 2004	Date of completion of the report 20 April 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer DAVID OLDE Telephone No. (02) 6283 2569

I. Basis of the report

1. With regard to the elements of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages 1-42, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages 43-45, received on 18 March 2005 with the letter of 17 March 2005
- [X] the drawings, pages 1/14-14/14, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the sequence listing part of the description:
  pages 1-8, as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims -	YES
	Claims 1-22	NO
Inventive step (IS)	Claims -	YES
	Claims 1-22	NO
Industrial applicability (IA)	Claims 1-22	YES
	Claims -	NO

2. Citations and explanations (Rule 70.7)

According to the Attorneys response and in light of the specification when read as a whole, the invention is seen to reside in an artificial chromosome comprising centromeric/neocentromeric DNA lacking α-satellite repeat DNA and containing an expressible heterologous nucleic acid. It appears that the neocentromeric region is transcriptionally active as it lacks α-satellite DNA. Said neocentromeric region is defined in humans as encompassed by S/MAR and comprising S/MAR, CENP-H, CENP-A, HP1α and other essential centromeric proteins (p.13 Lines 22-25).

Claims 1-7 relate to isolated nucleic acids comprising a nucleic acid corresponding to a centromeric or neocentromeric region of a higher eukaryotic chromosome comprising an expressible heterologous nucleic acid inserted in or proximal to said centromeric/neocentromeric region wherein the centromeric/neocentromeric is devoid of α-satellite DNA and the heterologous nucleic acid is expressed in a cell.

Claims 8-14 relate to an artificial or engineered chromosome comprising an expressible heterologous nucleic acid inserted in or proximal to a centromeric/neocentromeric region wherein the centromeric/neocentromeric is devoid of α-satellite DNA and the heterologous nucleic acid is expressed in a cell.

Claims 15, 16 are relate to modifying the phenotype of a eukaryotic cell by inserting a genetic sequence capable of modifying the genome of the cell into a centromeric or neocentromeric region of a chromosome or artificial chromosome wherein the centromeric/neocentromeric is devoid of α-satellite DNA and in the case of an artificial chromosome, inserting it into a cell.

Claims 17 and 18 relate to genetically modified eukaryotes comprising the artificial chromosome of claims 8 or 14 or having the modified phenotype of claims 15 or 16.

Claims 19-22 relate to methods of gene therapy comprising inserting a genetic sequence capable of modifying the genome of the cell into a centromeric or neocentromeric region of a chromosome or artificial chromosome wherein the centromeric/neocentromeric is devoid of α-satellite DNA, and in the case of an artificial chromosome, inserting it into a cell.

The following citations have been taken into account for the purposes of this opinion:

D1: US 6348353

D2: WO 2000 055325

D3: WO 1998 051790

D4: Wong *et al.* 2002. Gene Therapy. 9:724-726

D5: Saffery *et al.* 2001. PNAS. 98(10):5705-5710

Continued on Supplemental Sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

It is noted that the nucleic acid of claim 1 is not "isolated", yet the dependent claims refer to the "isolated" nucleic acid of claim 1. It may be that the term "isolated" was meant to be included in claim 1. Furthermore, as claimed the claim includes within its scope naturally occurring centromeric/neocentromeric regions which has implications with regard to novelty and inventive step.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D6: Willard *et al.* 2001. PNAS. 98(10):5374-5376

D7: Choo *et al.* 2001. TRENDS in Molecular Medicine. 7(6):235-237

D8: Saffery *et al.* 2002. Journal of Gene Medicine. 4(1):5-13

D9: Brown *et al.* 2000. TIBTECH. 18:218-223

NOVELTY(N) AND INVENTIVE STEP(IS)

Claims 1-22 are novel and inventive in light of D1, D2 and D9 as these citations disclose artificial chromosomes containing α-satellite DNA which is excluded from the applicant's claimed invention.

Claims 1-22 lack novelty and an inventive step in light of D3.

D3 discloses the isolation and characterisation of a region of human chromosome termed mardel 10 which is characterised as a neocentromere which contains no substantial α-satellite repeat DNA (p.3 Lines 19-30). Further disclosed is the use of this neocentromere in genetic constructs (artificial chromosomes) which also contain heterologous DNA encoding products of interest (p.21 Line 20 – p.22 Line 8, Examples 13-17), an origin of replication and telomeric sequences such that when introduced into a cell the chromosome is capable of replication and segregation. Also disclosed is the use of such artificial chromosomes in gene therapy.

D3 appears to disclose the applicant's neocentromere and its use in the production of artificial chromosomes for gene therapy. While the instant claims refer to specific genes and or binding proteins, it is considered that they are inherently present in the neocentromeric region characterised in D3. Hence these additional features do not distinguish the claimed invention from that of D3. Furthermore the heterologous gene need only be proximal to the centromeric region which is seen as encompassing the positioning of such a gene in the artificial chromosome of D3 (See for example pp13-23, Examples).Thus it appears that all the essential features of the applicant's claimed invention are disclosed. Hence claims 1-22 lack novelty.

Furthermore there does not appear to be any surprising properties attributable to applicant's invention that distinguish it from the disclosure of D3. Thus there is not considered to be any inventive merit in utilising known neocentromeric regions for their known properties. Hence claims 1-22 lack an inventive step in light of D3.

Claims 1-22 lack an inventive step in light of each of D4-D6.

D4-D6 each teach the use of mardel (10) neocentromeres in the production of artificial chromosomes which are suitable for the expression of heterologous genes to aid gene therapy and are substantially devoid of α-satellite DNA. While D4-D6 do not explicitly disclose a heterologous gene containing construct, they do teach that the minichromosomes would be suitable for such a use. Hence a PSA in light of the problem to be solved, seen as the identification of target areas within human chromosomes for the insertion and expression of heterologous genes, would be directly lead to the applicant's claimed invention from the teaching of each of D4-D6. Thus in the absence of surprising advantages or difficulties overcome by applicant's invention, the claimed invention lacks an inventive step in light of each of D4-D6.

Continued on Supplemental Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Claims 1-22 lack an inventive step in light of each of D7 and D8 when read in the light of D5.

D7 and D8 each provide a review of human artificial chromosomes and their importance in providing defined vectors for use in gene therapy. Each teach the use of neocentromeres lacking α-satellite DNA in the production of such vectors and refer to D5 for specific details in the construction of suitable vectors. Thus when the teachings of D7 or D8 are combined with that of D5, the claimed invention lacks an inventive step.

INDUSTRIAL APPLICABILITY(IA)

Claims 1-22 meet the requirements of the PCT in regard to industrial applicability.